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ALG-001075, THE PARENT OF PEVIFOSCORVIR SODIUM, EXHIBITS POTENT IN VITRO ANTIVIRAL PROPERTIES COMPARED TO OTHER HBV CAPSID ASSEMBLY MODULATORS IN CLINICAL DEVELOPMENT

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ALIGOS THERAPEUTICS

BACKGROUND

The hepatitis B virus (HBV) capsid is an attractive target for the treatment of chronic HBV infection.[1] Pevifoscorvir sodium (pevy, ALG-000184) is a prodrug of ALG-001075, a novel capsid assembly modulator leading to the formation of empty capsids (CAM-E).[2] Pevy has demonstrated potential best-in-class reductions of HBV DNA, RNA, HBsAg, HBeAg and HBcrAg in subjects with chronic HBV infection and is currently progressing through a phase 2 clinical trial.[3] Canocapavir (ZM-H1505R) and neracorvir (GST-HG141) are both CAM-E type capsid assembly modulators, currently in phase 2 clinical trials in China.[4,5]

AIM

The aim of this study was to compare the activity of ALG-001075 to canocapavir and neracorvir, two other CAMs in clinical development in China.

METHODS

HBV DNA antiviral activity (primary CAM mechanism of action (MoA)) was determined in HepG2.117 cells using quantitative PCR.[6] Effects on cccDNA establishment (secondary CAM mechanism) were assessed in HBV genotype D-infected HepG2-NTCP cells or primary human hepatocytes (PHH) by adding compound together with viral inoculum and measuring HBsAg as an indirect read-out. Direct effects on HBeAg (third CAM mechanism) were investigated in HBeAg-overexpressing cells. Further characterization was performed using immunofluorescent HBc staining in HepG2.117 cells.

RESULTS

1st MoA: ALG-001075, CANOCAPAVIR AND NERACORVIR INHIBIT HBV DNA PRODUCTION

ALG-001075, canocapavir and neracorvir inhibited HBV DNA production in HepG2.117 cells with EC_{50} values of 0.64, 5.8 and 24 nM, respectively.

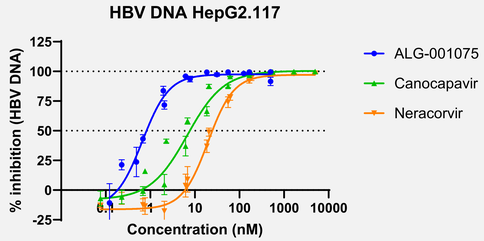

Figure 1. Dose-response curves for inhibition of HBV DNA replication in HepG2.117 cells. Curves and values represent mean ± SEM from 3 independent experiments.

2nd MoA: cccDNA ESTABLISHMENT IS EFFICIENTLY BLOCKED BY ALG-001075

The establishment of cccDNA in HepG2-NTCP cells or PHH was efficiently blocked by ALG-001075 (EC_{50} = 18 nM, as measured by HBsAg in HepG2-NTCP cells, and EC_{50} of 45 nM in PHH), but less so by neracorvir (EC_{50} = 3350 nM) and canocapavir (EC_{50} = ~1000 nM in PHH and > 5000 nM in HepG2-NTCP).

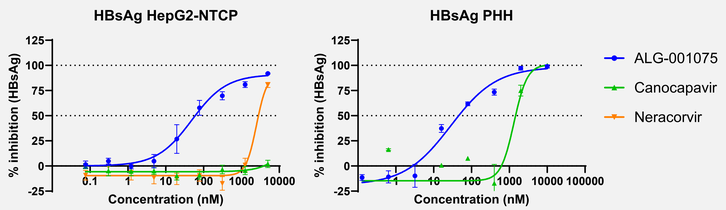

Figure 2. LEFT: Dose-response curves for inhibition of HBsAg production in HepG2-NTCP cells. Curves and values represent mean ± SEM from 3 independent experiments. RIGHT: Dose-response curves for inhibition of HBsAg production in HBV-infected primary human hepatocytes (PHH). Values represent mean ± SEM from 1 experiment.

3rd MoA: ALG-001075 IS MORE POTENT ON DIRECT INHIBITION OF HBeAg SECRETION

Inhibition of HBeAg secretion was measured in a cell line overproducing HBeAg. ALG-001075 was more potent in the direct inhibition of HBeAg secretion (EC_{50} = 855 nM) than canocapavir (EC_{50} = 4680 nM) and neracorvir (EC_{50} = 3233 nM).[7]

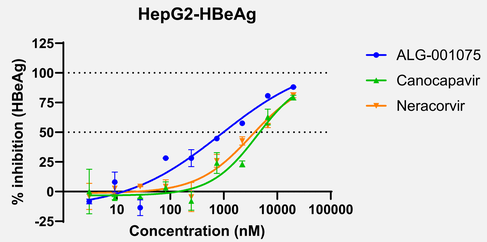

Figure 3. Dose-response curves for inhibition of HBeAg production in HepG2-HBeAg cells. Curves and values represent mean ± SEM from 1 experiments.

THE POTENCY OF ALG-001075 IS INFLUENCED BY THE T33N MUTATION

The HBV core protein mutation T33N is a major viral resistance mutation for 1st generation CAMs and reduces the activity of ALG-001075 in vitro: 27- and 23-fold for HBV DNA and HBeAg, respectively. However, to date, T33N has not been detected in subjects with chronic HBV infection treated with pevy for up to 96 weeks. Interestingly, canocapavir was not affected by T33N but was sensitive to Y118F (18-fold shift), while ALG-001075 was not affected by Y118F.

Table 1. Antiviral activity of ALG-001075 and canocapavir against CAM resistance mutations on HBeAg

Mutation	Fold Resistance	
	ALG-001075	canocapavir
T33N	23	1
Y118F	1	18

ALL THREE CAMS SHOW A CLEAR CAM-E PHENOTYPE

All 3 CAMs showed the typical CAM-E phenotype (no nuclear aggregates, some cytoplasmic accumulation) in immunofluorescent HBc staining assays.

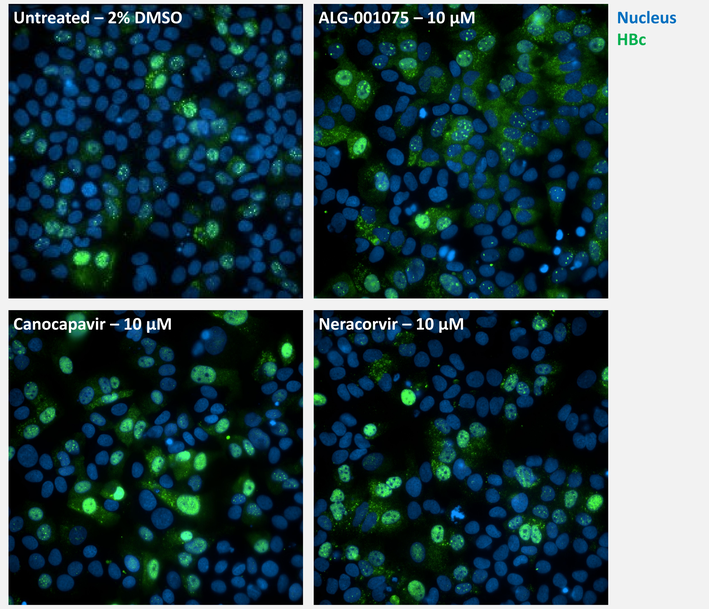

Figure 4. Immunofluorescent staining of HepG2.117 cells for HBc after treatment with different CAMs; nucleus in blue and HBc in green.

CONCLUSIONS

- **ALG-001075, the parent of pevy, displayed a highly potent in vitro antiviral profile, confirming its potential as a best-in-class CAM. It potently inhibits HBV DNA production, cccDNA establishment and HBeAg secretion. T33N, a prevalent CAM resistance mutation, only has a moderate impact on its antiviral activity.**
- **Canocapavir and neracorvir also inhibit HBV DNA production and HBeAg secretion but are less potent than ALG-001075. Their effects on cccDNA establishment in vitro are limited.**
- **Pevy is currently being developed as a monotherapy for the suppression of chronic HBV infection.**

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